
Clinical Study Protocol

A Placebo Controlled, Double Blind Investigation of the Therapeutic Utility of Xolair [Omalizumab] for Attenuating Aspirin Induced Bronchospasm in Patients With Aspirin Exacerbated Respiratory Disease (AERD) Undergoing Aspirin Desensitization

Amendment 2

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Phase: IV

Release date: January 16, 2013

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PROTOCOL SYNOPSIS

Patients with aspirin exacerbated respiratory disease (AERD) are at risk for serious bronchospasm when undergoing aspirin desensitization. In this study, Xolair [Omalizumab] will be administered for 16 weeks in a double blind, placebo controlled study to determine whether Omalizumab is associated with statistically significant attenuation of bronchospastic reaction during aspirin desensitization.

Despite use of medications associated with lessening of aspirin-induced bronchospasm (1-9), severe bronchospasm may still occur during aspirin desensitization. For this reason, patients currently must undergo aspirin desensitization in a setting with the capacity for close monitoring and presence of personnel and equipment necessary to manage severe and rapidly progressive bronchospastic reaction. Aspirin desensitization is generally performed in an inpatient setting. Administration of Omalizumab has the potential to favorably alter this situation by blocking significant bronchospastic reaction, and may permit aspirin desensitization to be done in outpatient settings.

Title of Study:

A placebo-controlled, double-blind investigation of the therapeutic utility of Xolair [Omalizumab] for attenuating aspirin induced bronchospasm in patients with aspirin exacerbated respiratory disease undergoing aspirin desensitization

Objectives:

The primary aim of this study is to examine the effect of Omalizumab on aspirin-induced bronchospasm occurring during aspirin desensitization in patients with AERD. Secondary objectives include assessment of aspirin dose which provokes respiratory reaction, proportion of subjects with declines in FEV1 of 20% and of 40%. We also will measure change in serum and urinary markers of eosinophil activation in association with Omalizumab treatment and aspirin desensitization, and degree of change in urinary LTE4 during aspirin challenge and with aspirin induced bronchospasm.

Study Rational:

Aspirin desensitization offers patients with AERD opportunity for benefit including reduced symptoms, medication reliance, and improved quality of life; however, due to risk for serious bronchospasm, aspirin desensitization is not widely available or commonly performed. We propose to assess the hypothesis that Omalizumab administration can reduce severity of aspirin-induced bronchospasm. The CDC (www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma/asthma.htm) estimates 68 per 1,000 adult Americans 18 years and over (14 million) currently have asthma. The corresponding estimate based on these data is that there are as many as 1.4 million adult Americans with AERD (10). If our hypothesis is confirmed, Omalizumab would have substantial utility for management of this large subgroup of asthmatics, and would lead to aspirin desensitization being performed more frequently.

Methodology:

This is a double-blind placebo controlled study.

Number of Centers & Patients:

Cleveland Clinic Foundation

N = 21

Population:

Patients with aspirin exacerbated respiratory disease (AERD) who are candidates for aspirin desensitization, and who fulfill criteria for Omalizumab.

Investigational Drug:

Xolair (Omalizumab)

Reference Therapy:

Placebo

Study Duration:

Omalizumab will be administered for 16 weeks. Within 1-3 weeks after this treatment is completed, patients will undergo aspirin desensitization. Patients will also accomplish a visit one month after initiation of aspirin desensitization treatment for final assessments. The total duration for subject participation is approximately 24 weeks (6 months).

Evaluation Criteria:

The primary outcome of interest is aspirin-induced respiratory reaction, as defined by the decline in the forced expiratory volume in one second (FEV₁) values from baseline to after ASA provoked reaction, in patients receiving Omalizumab vs. placebo. Secondary outcomes include: dose of aspirin that provokes the first respiratory reaction, the proportion of subjects with a decline in FEV₁ greater than 20% (significant respiratory reaction) and greater than 40% (severe respiratory reaction) through the course of desensitization. We also will measure: a) changes in serum and urinary markers of eosinophil activation in association with 16-week trial of Omalizumab and aspirin desensitization; b) changes in urinary LTE₄ in subjects previously treated with Omalizumab vs. placebo with aspirin challenge and aspirin-induced bronchospastic reaction.

Study Timetable

Duration of participation = Approximately 24 weeks (6 months)

- Phase A: Entry
- Phase B: Xolair/Placebo (approximately 16 weeks)
- Phase C: Aspirin Desensitization (1-3 weeks after Phase B)
- Phase D: Aspirin Desensitization Treatment (approximately 1 month after Phase C)

Study Phase	A	B	B	B	B	B	B	B	B	C	D
Injection schedule Q 2 week VS Q 4 week	Both	Both	Q 2 week	Both	Q 2 week	Both	Q 2 week	Both	Q 2 week	Both	Both
Time of Visit	Screening	Baseline	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Desens	Final Visit
Inclusion/Exclusion criteria	x										
Information & Informed consent	x										
History and Physical exam	x			Q 4 week only	x			Q 4 week only	x	x	x
QOL questionnaires	x									x	x
Spirometry	x	x		x		x		x		x	x
Laboratory samples	x									x	x
Adverse events		x	x	x	x	x	x	x	x	x	x
Administration of Xolair or placebo		x	x	x	x	x	x	x	x		

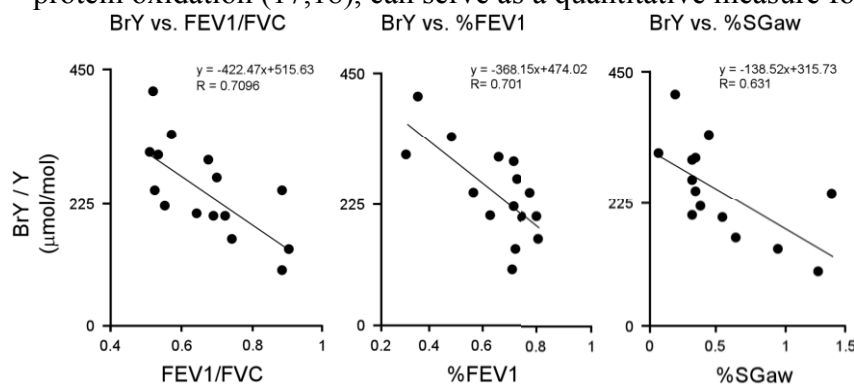
All visits have a window of +/- 7 days

1 INTRODUCTION

Omalizumab was recently approved by the FDA for management of patients with moderate-severe asthma, who are not achieving the goals of asthma management despite pursuing appropriate avoidance measures and taking regular “controller” medications. Based on evidence demonstrating its utility for improving asthma outcomes and reducing medication reliance (11, 12), this humanized monoclonal anti-IgE antibody has been welcomed enthusiastically by the Allergy/Immunology community. The anti-inflammatory effects of Omalizumab were recently demonstrated in a study by Djukanovic, et al (13), who carried out a randomized, double blind, placebo-controlled trial of 45 mild-moderate asthmatics with sputum eosinophilia $\geq 2\%$. Bronchial biopsies performed after 16 weeks of treatment revealed a significant decline in IgE in epithelium and submucosa in association with Omalizumab. In addition, a significant decline in eosinophils in epithelium and submucosa was observed. The latter finding is relevant for patients with AERD, as aspirin-provoked reaction occurs due to release of higher levels of leukotrienes and greater end-organ responsiveness to leukotrienes (3). It follows that a dramatic decline in eosinophils encouraged by exposure to Omalizumab for 16 weeks would lead to a substantial and clinically significant reduction in the capacity for leukotriene release, thereby reducing severity of aspirin-provoked bronchospastic reaction.

We propose to examine the impact of Omalizumab administration for 16 weeks in patients with AERD on attenuating aspirin induced bronchospasm. We also will assess eosinophilic inflammation by measuring plasma and urine levels of 3-bromotyrosine (BrTyr) and 3, 5-dibromotyrosine (Br2Tyr). Previous studies (14,15) have shown that eosinophil activation promotes formation of brominating oxidants in allergen challenged subjects leading to post translational modification of proteins forming the stable molecular markers BrTyr and Br3Tyr. Furthermore, BrTyr levels are elevated (16) in plasma, airway lining fluid, and urine in patients with severe asthma. Recent studies also demonstrate strong inverse correlations between systemic levels of plasma BrTyr and multiple measures of airflow limitation (Fig. 1).

Thus, measurements of BrTyr and Br2Tyr, products specific for eosinophil peroxidase-catalyzed protein oxidation (17,18), can serve as a quantitative measure for assessing the efficacy of aspirin



desensitization and Xolair (Omalizumab) effect in patients with AERD. Similarly, since enhanced oxidant stress following eosinophil activation syndromes and allergen challenge has been observed, a global systemic indicator of oxidant stress, such as urinary isoprostanes, a free radical generated product of arachidonic acid (19), may also prove informative as a quantitative index with which to monitor efficacy of Xolair (Omalizumab) effect in patients with AERD.

BACKGROUND

The initial report of aspirin intolerance appeared more than a century ago, only 3 years after aspirin was synthesized (20). Fatal reactions from aspirin were described in the 1930s (21,22). However, it was not until 1968 that Samter and Beers (23) described a clinical “triad” of nasal polyposis, bronchial asthma, and “life threatening reactions to acetylsalicylic acid” as a clinical syndrome.

We now recognize that patients with this condition exhibit an aggressive inflammation of the upper and lower airways (24), for which provocation of asthma with/without nasal/ocular symptoms after ingestion of aspirin (and other non-steroidal anti-inflammatory drugs) is a marker. Despite avoidance of aspirin and cross-reacting drugs, this subgroup of patients may experience refractory rhinosinusitis and asthma – frequently requiring numerous sinus-surgery procedures and regular administration of oral steroids. The syndrome of aspirin sensitivity affects an estimated 4-10% of adult asthmatics (10). Once aspirin sensitivity develops, it is present for the rest of the patient’s life.

The term “desensitization” has traditionally been used to describe a procedure that involves modification of IgE-mediated (allergic/anaphylactic) potential to a substance – usually a drug such as penicillin, via repetitive re-exposure in a graded-dose fashion (25). Widal managed a patient in 1922 (26), with gradually increasing doses of aspirin, such that instead of reacting to aspirin when the previously-established provoking dose was administered, this individual was able to tolerate aspirin, given in advancing doses, without adverse reaction. Zeiss and Lockey (27) observed the same phenomenon of aspirin “desensitization”, and ultimately this procedure was utilized to allow individuals with AERD who require aspirin (or an aspirin-like drug) for treatment of arthritis or cardiovascular conditions to safely take aspirin without adverse reaction.

The aspirin desensitization procedure, in which a state of “tolerance” can be induced and maintained, entails administration of incremental oral doses of aspirin over the course of several days, until a dosage of 650 mg (2 tablets) of aspirin can be taken without adverse reaction. Because aspirin-provoked reaction may be delayed for 2-3 hours, the minimum interval between doses of aspirin is 3 hours; for this reason, the challenge may span 3-4 days. After doses of aspirin are given at 8:00 a.m., 11:00 a.m., and 2:00 p.m., the challenge is suspended until the following day. Patients admitted for observation to undergo the procedure are released at approximately 5-6 PM, and return the following morning to continue the desensitization. Aspirin desensitization entails provoking respiratory reaction to aspirin, then administering the same dose that provoked this reaction, such that an individual may have repeated reactions to the same dose. When an aspirin-sensitive individual no longer reacts to this dose, the aspirin dosage can be increased as specified in our protocol (shown below) until 650 mg of aspirin can be taken without untoward reaction. The sequence of aspirin doses should be regarded as a general guide. The schedule is modified for each patient based on the reaction(s) to aspirin that take place during the procedure. The dosage at which each AERD patient will react to aspirin, the number of reactions at each dose, and whether reaction occurs at multiple dosage levels are quite variable. For this reason, the number of challenge doses that will be required, and the duration of the desensitization, cannot be predicted *a priori*. In most cases, the procedure spans 3-4 days.

Aspirin dosages

30 mg

60 mg

100 mg

150 mg

325 mg

650 mg

End!

Aspirin desensitization can be perpetuated indefinitely if aspirin is taken on a daily basis.

Bronchospastic reaction in AERD patients results from enhanced release of leukotrienes provoked by aspirin (28), in combination with greater target organ sensitivity to leukotrienes (29). Aspirin-provoked bronchospasm can be lessened by administration of anti-leukotriene drugs (4); however, the protection is not complete, and the response is heterogeneous (3). The effect of anti-leukotrienes appears to be to shift the dose-response curve to the right, and a tendency to transfer aspirin-provoked reaction to the upper airway (4). Bronchospasm has also been lessened in AERD patients by pre-treatment with cromolyn (5,6), nedocromil (6), salmeterol (7), clemastine (8), and inhaled steroid (9). However, despite use of combination “controller” agents, aspirin provoked reaction can be volatile and may entail life-threatening bronchospasm. We have recently desensitized a patient who exhibited profound bronchospasm (shown in Figure 2) despite receiving oral steroid burst/taper prior to the procedure, taking regular inhaled steroid combined with long acting beta agonist, and montelukast at higher than standard dosage (30 mg/day). This case illustrates the ongoing need for a therapeutic intervention that can reliably block bronchospastic reaction during aspirin challenge/desensitization.

Because serious bronchospasm may occur at any time during aspirin desensitization, this procedure needs to be performed in a monitored setting. At The Cleveland Clinic Foundation, this procedure is performed in our Short-Procedure Unit, where respiratory reactions can be promptly treated, a one-on-one physician/nurse to patient ratio can be maintained throughout the procedure, and emergency-resuscitative equipment and trained personnel are readily available. We also stipulate that aspirin-sensitive patients undergo this procedure at a time when their asthma is well controlled. In order to proceed, FEV1 should be greater than 70% predicted (or prior best measurement). In order to ensure the reliability of our findings, we also will be including two placebo doses at the start of day#1, so that individuals whose lung function declines due to unstable asthma (or situational factors) can be identified. Such reactions would obfuscate interpretation of our findings if they were misclassified as bonafide reactions to aspirin.

Two decades ago, the first double-blind, placebo-controlled, crossover study of aspirin treatment during the desensitized state was reported (30). In two-thirds of aspirin-sensitive subjects, statistically significant improvement was observed in nasal/sinus symptoms and medication reliance for rhinosinusitis in association with regular administration of aspirin after desensitization was achieved. Sweet, et al. (31) described results of a long-term assessment of the therapeutic utility of aspirin desensitization in 35 patients followed for an average of 3.7 years, and compared their outcomes with 42 AERD patients who avoided aspirin while not undergoing desensitization and were used as controls. Aspirin desensitization was associated

with statistically-significant reduction in hospitalization rates and emergency-department utilization, annual numbers of outpatient visits, episodes of sinusitis and antibiotics required, need for polypectomy and sinus-surgery procedures. Benefit has been more dramatic for rhinosinusitis than for asthma. However, aspirin desensitization may also be considered for patients with AERD with recalcitrant asthma; in one half of 500 AERD patients in a large European study (32), asthma was severe and steroid-dependent. For this reason, such patients also may be viewed as candidates for aspirin desensitization treatment.

In summary, AERD may appear only after years of progression of rhinosinusitis and asthma. The aggressive upper and lower airways inflammation characteristic of this condition continues despite avoidance of aspirin and aspirin-like drugs. Aspirin desensitization can be carried out as a means to reduce symptoms and medication reliance. This procedure can be justified based on the substantial improvement in health service utilization and quality-of-life that will result. Following the procedure, patients typically continue to require regular medication for asthma and nasal/sinus symptoms, albeit at lower doses and reduced frequency of administration. The economic savings associated with aspirin-desensitization treatment accrue from reduced rates of hospitalization and sinus-surgery procedures; re-operative intervention can be reduced from an average of once every three years (before desensitization) to once every ten years during long-term daily treatment with aspirin. An intervention that would make aspirin desensitization more widely available, by reducing risk (for severe bronchospasm) associated with this procedure, has substantial potential for improving health care outcomes and quality of life for AERD patients.

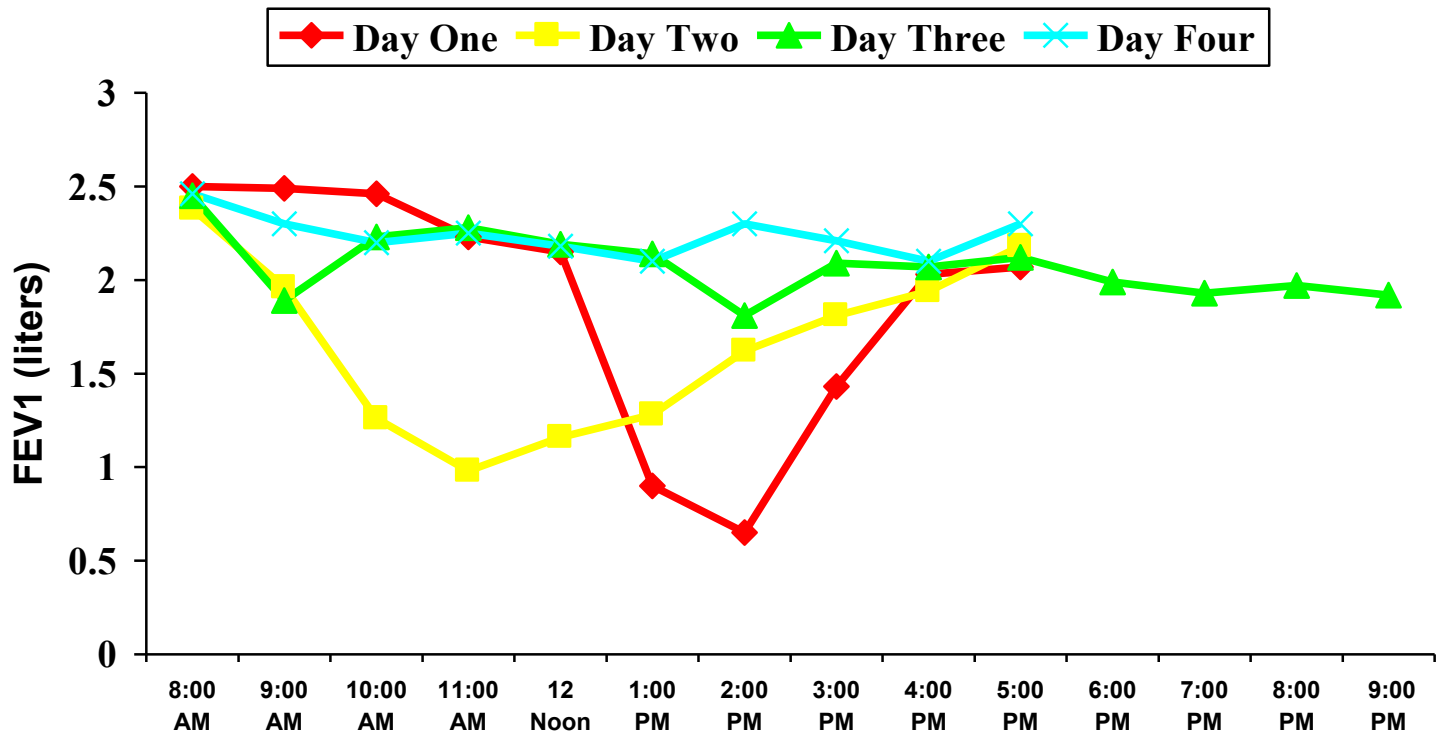


Figure 2: Serial FEV1 measurements are displayed for JN, who underwent successful aspirin desensitization but had severe bronchospastic responses to graded dose aspirin challenge. On day 1 (shown in red), 60 mg aspirin challenge dose was associated with 64% decline in FEV1, which continued to decline further despite administration of nebulized beta agonist and then nebulized beta agonist combined with anticholinergic agent. Repeated nebulized beta agonist and nebulized corticosteroid were administered along with intramuscular epinephrine, oral anti-leukotriene, intravenous magnesium and intravenous corticosteroid. Lung function improved over several hours. On day 2 (shown in yellow), 60 mg dose was repeated and this provoked 59% decline in FEV1. Protracted bronchospasm continued for the rest of day 2 despite administration of nebulized, oral, and intravenous medications. On day 3, 60 mg aspirin dose was tolerated without untoward reaction, and then aspirin dosage was advanced per protocol without further reactions. This patient continues to take aspirin daily, and has experienced benefit in the course of AERD in recent months.

2 STUDY OBJECTIVES

PRIMARY AIM:

To assess the impact of Omalizumab on aspirin-induced bronchospasm occurring during aspirin desensitization in patients with AERD.

PRIMARY OUTCOME OF INTEREST:

Aspirin-induced respiratory reaction as defined by the decline in the forced expiratory volume in one second (FEV₁) values from baseline to after ASA provoked reaction.

SECONDARY OUTCOMES OF INTEREST:

1. Dose of ASA that provokes the first respiratory reaction.
2. Proportion of subjects with a decline in FEV₁ greater than 20% (significant respiratory reaction) through the course of the desensitization process.
3. Proportion of subjects with a decline in FEV₁ greater than 40% (severe respiratory reaction) through the course of the desensitization process.
4. Change in plasma and urinary markers of eosinophil activation in association with 16-week trial of Omalizumab and aspirin desensitization, compared with placebo.
5. Change in urinary LTE₄ in subjects previously treated with Omalizumab vs. placebo with aspirin challenge and aspirin-induced bronchospastic reaction.

3 INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN

Design:

The study will be a randomized double-blind placebo-controlled evaluation of the impact of Omalizumab on aspirin desensitization in patients with AERD. Patients who are candidates for aspirin desensitization will be offered the opportunity to participate in this study, and will receive either Omalizumab or identical placebo. Subjects will receive 4 injections every 4 weeks or 8 injections every 2 weeks (+/- 7 days) for approximately 16 weeks (based on serum

IgE and body weight according to Xolair label), after which aspirin desensitization will be performed.

Vital signs (including pulse oximetry) will be measured and recorded at baseline, prior to each dose of aspirin, and prn symptoms. Serial spirometry will be measured at baseline each morning, every hour during the course of the desensitization procedure, and prn respiratory symptoms. The completion time for each challenge day will vary based upon the timing of aspirin-provoked reaction and response to treatment; however, we anticipate that on most days the challenge will conclude between 5:00 and 6:00 PM -- 3 hours following the last dose of aspirin, or after recovery from aspirin provoked bronchospasm.

AERD patients (N = 21) will be randomized 2:1 to receive either Omalizumab or placebo for a period of approximately 16 weeks prior to aspirin desensitization procedure.

We will also address the hypothesis that the potential for eosinophil activation and leukotriene release during aspirin induced reaction will be significantly reduced in association with Omalizumab by performing serial measurements of plasma and urinary Borty, F2Isoprostanes and serial measurements of urinary LTE4.

Aspirin-provoked reaction in patients with AERD occurs due to heightened leukotriene release and greater end-organ responsiveness to leukotrienes (28,29). Omalizumab administration for 16 weeks is associated with a significant decline in eosinophils in epithelium and submucosa (13). We hypothesize that a substantial and clinically significant reduction in the capacity for leukotriene release will be promoted by the dramatic decline in eosinophils resulting from treatment with Omalizumab, and that this will significantly reduce severity of aspirin-provoked bronchospastic reaction. We will measure serum and urinary markers of eosinophil activation, as well as urinary LTE4 at the following time points to confirm our hypothesis:

Measurements of plasma and urinary markers will be performed:

- At baseline, prior to randomization to Omalizumab/placebo (plasma and urine)
 - At baseline, prior to aspirin desensitization procedure
 - 3 hours after aspirin dose 1-3 (urine)
 - 3 hours post reaction specimen (plasma and urine)
 - After completion of aspirin desensitization
 - 3 hours following dose of 650 mg (plasma and urine)
 - 1 month follow-up visit after taking aspirin 650 mg BID daily (plasma and urine).
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- We will obtain samples at initiation of aspirin desensitization to assess impact of Omalizumab exposure compared with placebo for the prior 16 weeks.
 - Serial samples of urine will be obtained on day 1 of desensitization to examine the impact of aspirin challenge doses (without and with reaction) in patients who have received Omalizumab compared with placebo. Samples will be obtained on day 2 in those in whom respiratory reaction did not occur on day 1.
 - Samples obtained at desensitization will also be compared in subjects randomized to Omalizumab vs. placebo; these specimens will also be used as “baseline” for aspirin desensitization treatment.
 - Final samples of blood and urine will be obtained at visit 11, after 1 month of aspirin desensitization treatment, to assess the effect of aspirin desensitization treatment with and without prior administration of Omalizumab.

3.2 STUDY POPULATION

We intend to offer participation to all patients with AERD seen at the Cleveland Clinic Foundation

- Patients will fulfill the following criteria, according to Xolair label:
 - AERD – confirmed by history and clinical course
 - Atopic as determined by immediate hypersensitivity skin testing or RAST.
 - IgE level = 30-700 IU/ml
 - Candidate for aspirin desensitization

Participants will be randomized 2:1 (14:7) to receive either Omalizumab or placebo for a period of 16 weeks prior to aspirin desensitization procedure.

Inclusion criteria

- Age \geq 18 years.
- Fulfill diagnostic criteria for AERD and be a candidate for aspirin desensitization
 - Chronic asthma – frequently moderate-severe or severe
 - patients will have a history compatible with variable airflow obstruction (33).
 - Chronic rhinosinusitis – usually requiring previous sinus surgery procedure(s).
 - Sinusitis will have been confirmed by computed tomography presently and/or in the past.
 - History of adverse reaction to aspirin and/or aspirin-like drugs (e.g., ibuprofen, naproxen, etc.) compatible with AERD.
- Candidate for Xolair [Omalizumab]
 - Moderate-severe persistent asthma
 - IgE = 30-700 IU/ml
 - IgE mediated (allergic) potential to inhalant allergen(s) by cutaneous or in vitro testing.

Exclusion criteria

- Women of childbearing potential not using appropriate contraception method(s)
- Women currently breastfeeding
- Women who desire to become pregnant during the time of participation in this study
- Men who desire to get someone pregnant during participation in this study
- Known sensitivity to Xolair [Omalizumab]
- Treatment with Xolair (Omalizumab) in the past 12 months
- IgE level < 30 IU/ml, or > 700 IU/m.
- No evidence of atopy by immediate hypersensitivity skin testing
- Use of any other investigational agent in the last 30 days
- Age < 18 year.
- Current tobacco habituation
- Presence of emphysema
- Ethanolism or drug abuse within last 12 months
- Presence of significant medical condition including malignancy, neurologic, kidney, gastrointestinal, liver or cardiovascular disease

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- Contraindication for aspirin administration, including but not limited to: severe anemia, thrombocytopenia, recent gastrointestinal hemorrhage. CBC will be obtained if not recently performed
 - Extensive travel commitments during the study that would interfere with study measurements or clinic visits

3.3 TREATMENTS

INVESTIGATIONAL THERAPY AND REFERENCE THERAPY

Patients with AERD who are candidates for aspirin desensitization will be offered the opportunity to participate. Once enrolled, patients will receive either Omalizumab (administered according to Xolair label) or identical placebo. Subjects will receive 4 injections every 4 weeks or 8 injections every 2 weeks (+/- 7 days) for approximately 16 weeks, after which aspirin desensitization will be performed. Desensitization procedure will be carried out per protocol, as detailed above. Aspirin provoked reaction necessitates treatment with reversal of bronchospasm, followed by re-introduction of the same dose. Dosage advancement may proceed if this dose is then tolerated without untoward reaction. As more than 1 reaction may occur, the desensitization procedure typically spans 3-4 days.

TREATMENT, ASSIGNMENT, BLINDING AND RANDOMIZATION

Patients will be randomized 2:1 to receive either Omalizumab or placebo for a period of 16 weeks prior to aspirin desensitization procedure. Randomization will be performed by John Petrich of the Pharmacy Department.

The randomization code may be broken by the investigator only in a medical emergency. Should this be required, the reasons for this will be documented.

CONCOMITANT THERAPY

Participants may receive medications as appropriate for management of AERD, including but not limited to agents to treat asthma and rhinosinusitis. Efforts will be made to maintain medications at constant doses during participation, and to avoid adding additional medications or modifying dose of current medications -- unless required for exacerbation of asthma and/or rhinosinusitis. Subjects will diligently avoid aspirin and aspirin-like drugs prior to desensitization.

INTERRUPTION OR DISCONTINUATION OF TREATMENT

Every patient has the right to discontinue study participation at any time, and patients may be discontinued from the study for any reason beneficial to his/her wellbeing. All data generated up to the time of discontinuation from the study will be analyzed and the reason(s) for discontinuation will be recorded.

TREATMENT COMPLIANCE

In order to continue participation in the study, patients must be adherent with the recommended schedule for administration of drug/placebo for 16 weeks. Also, patients should schedule aspirin desensitization within the 2-3 week period following the final scheduled dose of drug/placebo.

3.4 VISITS AND ASSESSMENTS

Study Timetable

Duration of participation = approximately 24 weeks (6 months)

- Phase A: Entry
- Phase B: Xolair/Placebo (approximately 16 weeks)
- Phase C: Aspirin Desensitization (1-3 weeks after Phase B)
- Phase D: Aspirin Desensitization Treatment (approximately 1 month after Phase C)

Study Phase	A	B	B	B	B	B	B	B	B	C	D
Injection schedule Q 2 week VS Q 4 week	Both	Both	Q 2 wee k	Both	Q 2 week	Both	Q 2 week	Both	Q 2 wee k	Both	Both
Time of Visit	Screenin g	Baseline	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Desens	Final Visit
Inclusion/Exclusion criteria	x										
Information & Informed consent	X*										
History and Physical exam	x			Q 4 week only	x			Q 4 wee k only	x	x	x
QOL questionnaires	x									x	x
Spirometry	x	x		x		x		x		x	x
Laboratory samples	x									x	x
Adverse events		x	x	x	x	x	x	x	x	x	x
Administration of Xolair or placebo		x	x	x	x	x	x	x	x		

All visits have a window of +/- 7 days

*** Informed consent may take place prior to Phase A, while the patient is completing an outpatient visit.**

Phase A - Enrollment

Visit 1:

- Verify that inclusion criteria are fulfilled
- History and Physical exam
- Baseline spirometry performed
- Baseline QOL obtained

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- Baseline specimens of blood and urine for eosinophil activation markers (plasma bromotyrosine (BrTyr) and dibromotyrosine (Br2Tyr), and urinary BrTyr and F2Isoprostanes (F2IsoP) obtained.
 - Urine for LTE4
 - IgE level obtained if not performed previously.
 - Urine pregnancy test

Phase B – Xolair/Placebo

Baseline:

- Xolair/ placebo initiated (anticipate q 2 weekly administration for most subjects)
- Spirometry
- Injectable epinephrine dispensed.

Week 4, 8, and 12 (receiving injections every 4 weeks +/- 7 days):

- Xolair/ placebo dosing
- Spirometry
- Physical Examination (weeks 4 and 12)

Week 2, 4, 6, 8, 10, 12, 14 (receiving injections every 2 weeks +/- 7 days):

- Xolair/ placebo dosing
- Spirometry at weeks 4, 8, 12
- Physical Examination (weeks 6 and 14)

Phase C – Aspirin Desensitization

spans 3-4 days

Day 1

- History and Physical exam
- Vital signs (including pulse oximetry) will be measured and recorded at baseline, prior to each dose of aspirin, and prn symptoms
- Spirometry performed at baseline, hourly, and prn symptoms during aspirin desensitization procedure, per protocol
- QOL obtained to assess benefit on Omalizumab vs. placebo compared with baseline.
- Blood and urine for eosinophil activation markers and urinary LTE4 obtained prior to aspirin challenge: these will reflect post-Omalizumab and baseline desensitization specimens.

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- Two placebo doses will be given to ensure that lung function is stable ($< 10\%$ variability in FEV1 compared with baseline) prior to proceeding with aspirin challenge.
 - Urinary LTE4, BrTyr, and F2IsoP obtained 3 hours post aspirin dose 1.

Day 2

- History and Physical exam
- Vital signs (including pulse oximetry) will be measured and recorded at baseline, prior to each dose of aspirin, and prn symptoms
- Spirometry performed at baseline, hourly, and prn symptoms during aspirin desensitization procedure, per protocol
- Urinary LTE4, BrTyr, and F2IsoP obtained 3 hours post aspirin doses 2 and 3.
- Plasma BrTyr, Br2Tyr, and urinary BrTyr, F2IsoP and LTE4 obtained 3 hours post reaction (if no reaction following doses 1-3)

Day 3 or 4 – post desensitization sample (3 hours after 650 mg ASA dose)

- History and Physical exam
- Vital signs (including pulse oximetry) will be measured and recorded at baseline, prior to each dose of aspirin, and prn symptoms
- Spirometry performed at baseline, hourly, and prn symptoms during aspirin desensitization procedure, per protocol
- Plasma BrTyr, Br2Tyr, and urinary BrTyr, F2IsoP and LTE4 obtained 3 hours post reaction (if no reaction following doses 1-4)
- Blood and urine for eosinophil activation markers and urine for LTE4, BrTyr, and F2IsoP obtained: these are post-aspirin desensitization samples.

Phase D – Aspirin Desensitization Treatment

Final Visit

- 1 month (+/- 7 days) post-desensitization: final assessments and labs obtained
- History and Physical exam
- Progress spirometry performed to assess change with aspirin desensitization treatment.
- Blood and urine for eosinophil activation markers: Plasma BrTyr, Br2Tyr, and urinary BrTyr, F2IsoP.
- urine for LTE4
- QOL obtained to assess benefit on aspirin desensitization treatment.
- urine pregnancy test

Laboratory Tests

Primary Aim

Our primary aim is assess the impact of Omalizumab on aspirin-induced bronchospasm occurring during aspirin desensitization in patients with AERD. The primary outcome of interest is bronchospastic reaction induced by aspirin. This will be quantified by the decline in the forced expiratory volume in one second (FEV₁) values from baseline to after aspirin-provoked reaction.

Secondary Aim

We will assess whether Omalizumab attenuates aspirin induced bronchospasm by examining the dose of aspirin provoking respiratory reaction, and by analyzing the proportion of subjects who experience bronchospastic reaction with declines in FEV₁ $\geq 20\%$ and $\geq 40\%$, respectively, in Omalizumab and placebo groups.

We also will measure markers of eosinophil activation and urinary LTE₄, to confirm our hypothesis that aspirin-provoked reaction will be significantly attenuated by prior administration of Omalizumab for 16 weeks. We anticipate that systemic markers of eosinophil activation will be elevated in all AERD subjects at baseline, and that a reduction will be observed in Omalizumab-treated patients in the baseline sample at time of desensitization compared with placebo. This may also be observed in the level of urinary LTE₄ compared with initial sample at study entry, and compared with placebo-treated subjects -- among whom this should be relatively unchanged. If a dramatic decline in eosinophils (and consequent reduction in potential for leukotriene release) is achieved with Omalizumab treatment for 16 weeks (13), we would expect this to also be reflected in significant reduction in the rise in urinary markers of eosinophil activation and oxidant stress (BrTyr and F₂IsoP), as well as LTE₄, with aspirin-induced respiratory reaction in subjects randomized to Omalizumab compared to placebo. At the one month follow up visit, we expect that we will find a reduction in systemic markers of eosinophil activation in placebo-treated patients compared with baseline sample obtained at study entry in association with aspirin desensitization treatment, but that this will be less marked compared with those randomized to prior treatment with Omalizumab.

Markers of eosinophil activation and urinary LTE₄ will be measured as previously reported (14, 18, 19, 34).

3.5 SAFETY ASSESSMENTS

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, as described in the study manual.

An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy). Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

A serious adverse event is an undesirable sign, symptom or medical condition which: 1. is fatal or life-threatening, 2. required hospitalization, 3. results in persistent or significant disability/incapacity, 4. is medically significant, in that it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

4 DATA MANAGEMENT AND STATISTICAL METHODS

Safety Assessment:

Investigators will enter information required by the protocol into the Case Report Forms (CRFs). Non-obvious errors or omissions will be entered on Data Query Forms, which will be returned to the investigational site for resolution. The assessment of safety will be based mainly on the frequency of adverse events, which includes all serious adverse events. Adverse events will be summarized by presenting for each treatment group the number and percentage of patients having any adverse event, having an adverse event in each body system, and having each individual adverse event. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.

Statistical Methods:

Unequal-variances t-tests will be used to compare the change in FEV₁ (and the aspirin provoking dose) between subjects who receive placebo and those who receive Omalizumab. If distributional assumptions are not met, the nonparametric Wilcoxon Rank Sum test will be used. Pearson's chi-square test will be used to test if the proportion of subjects with a decline in FEV₁ > 20% is significantly different between subjects who receive placebo and those who receive Omalizumab. A significance level of 0.05 will be used for all analyses. SAS 9.1 software, SAS Institute, Cary, NC will be used to perform all analyses.

Interim Analysis

An interim analysis will be conducted based on enrolled patient data through the last completed study visit. Primary and secondary outcome measures will be reviewed as part of the analysis. If there are no clinically meaningful findings, the interim analysis report will be submitted to the FDA with the annual report. If there are meaningful clinical findings, the PI will send a letter to the subjects detailing these findings. If the study continues, the statistician will further evaluate the sample size.

Sample Size Calculation:

No previous studies have been done to examine the impact of Omalizumab in the ASA desensitization process. Stevenson, et.al (1), conducted a study on the impact of Montelukast in inhibiting aspirin response in AERD patients. We believe the standard deviation for the change in FEV₁ values for both subject groups will be similar in magnitude to those previously observed (1); for this reason, we have based our sample calculations on these estimates. The standard deviation for the change in FEV₁ values is assumed to be equal to 6.7 and 7.8 for the placebo and Omalizumab groups, respectively. The minimum mean difference in the change in FEV₁ between the two groups that can be detected, with randomization proceeding 2:1 to Omalizumab and placebo groups, and with 14 and 7 AERD patients in each group (assuming an attrition rate of 3 subjects, or 14-15%), respectively, is 12.8%, with a power of 90%. Secondary outcomes of interest noted above will also be examined; however, the proposed enrollment may not entail sufficient power to assess these in a definitive fashion.

The objective of this trial is to study the therapeutic utility of Omalizumab for attenuating aspirin induced bronchospasm occurring during aspirin desensitization. Data will be summarized with respect to demographic and baseline characteristics and efficacy and safety observations. Exploratory analyses will be performed using descriptive statistics.

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Signature of Investigator(s) and Study Personnel

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	signature	date

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<i>type/print name</i> Medical Director	_____	_____
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<i>type/print name</i> (Regional Scientific Director)	_____	_____
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